Understanding Obesity Genes and Environment in the Determination of Body Weight

Prof. Rudy Leibel

Understanding Obesity Genes and Environment in the Determination of Body Weight

R. Leibel
Division of Molecular Genetics
and Naomi Berrie Diabetes Center
Columbia University

Why Is Body Weight (Fat Mass) Regulated?

UP
• Reproduction
• Environmental vicissitudes

DOWN
• Predator evasion

WAGES OF EVOLUTION
• Defense against loss of fat mass >> gain

Adiposity(u) = f(Q) – f(W)

Past

Present

The screen versions of these slides have full details of copyright and acknowledgements
Understanding Obesity Genes and Environment in the Determination of Body Weight
Prof. Rudy Leibel

Ligand Receptor Both
A0 A1 A2 B0 B1 B2 A0 + B0

Phenotype Phenotype mild severe gene environment

Ligand Receptor Both

X VMN: profound obesity
X LHA: anorexia, weight loss

Hormone secreted from fat in proportion to mass
= cell size x number

LEPTIN
Understanding Obesity Genes and Environment in the Determination of Body Weight
Prof. Rudy Leibel

Monogenic Forms of Obesity

**Human**
- Rare Leptin
- Rare POMC
- Rare MC4R

**Rodent**
- ob/ob
- db/db
- fat/fat

4-6% of severe human obesity

Barsh and Schwartz 2002
Understanding Obesity Genes and Environment in the Determination of Body Weight
Prof. Rudy Leibel

Multiple Biological Effects of Leptin in Humans

Before
Wt = 42 kg at 3 yrs

Farooqi et al., JCI. 2002;110:1093
and Farooqi et al., Nature 2001; 414:34

After
Wt = 31 kg at 7 yrs

Multiple Biological Effects of Leptin in Humans

LEPTIN RECEPTOR

Proband HD416

Barsh and Schwartz 2002

The screen versions of these slides have full details of copyright and acknowledgements
Understanding Obesity Genes and Environment in the Determination of Body Weight
Prof. Rudy Leibel

- Diagram of POMC showing weight trends in girls and boys.
- Chart showing age (months) vs. weight for girls and boys.

Patient A

- Photograph of a patient with marked obesity.

MC4R Mutations Result in a Dominantly Inherited Obesity Syndrome

- Chart showing mean ad libitum energy intake (KJ/kg lean mass).
- Graphs illustrating hyperphagia and increased bone mineral density.

The screen versions of these slides have full details of copyright and acknowledgements
Mutations in MC4R Represent the Commonest Monogenic Human Obesity Syndrome

Farooqi et al., NEJM 2003;348:1085-1095

Barsh et al., Nature 404:644, 2000

The screen versions of these slides have full details of copyright and acknowledgements
Understanding Obesity Genes and Environment in the Determination of Body Weight
Prof. Rudy Leibel

Dizygotic twins

Monozygotic twins

Mexican American

African American

<table>
<thead>
<tr>
<th>Gene</th>
<th>Obese</th>
<th>Lean</th>
<th>Obese</th>
<th>Lean</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ghrelin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPAR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EnkephalinB</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPY</td>
</tr>
<tr>
<td>Orphan receptors</td>
</tr>
</tbody>
</table>

The screen versions of these slides have full details of copyright and acknowledgements
Understanding Obesity Genes and Environment in the Determination of Body Weight
Prof. Rudy Leibel

Caucasian

<table>
<thead>
<tr>
<th>Gene</th>
<th>Adult</th>
<th>Child</th>
</tr>
</thead>
<tbody>
<tr>
<td>GPR4</td>
<td>obese</td>
<td>lean</td>
</tr>
<tr>
<td>GPR1</td>
<td>obese</td>
<td>lean</td>
</tr>
<tr>
<td>LEPR</td>
<td>Val81Ile</td>
<td></td>
</tr>
<tr>
<td>PPAR1</td>
<td>Gln223Arg</td>
<td></td>
</tr>
<tr>
<td>PPAR6</td>
<td>Leu656Asn</td>
<td></td>
</tr>
<tr>
<td>MC4R</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPAR</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BMI as a Function of Age, Sex, and rs7566605 Genotype

INSSG2 2q14.1-2


The screen versions of these slides have full details of copyright and acknowledgements
Understanding Obesity Genes and Environment in the Determination of Body Weight

Prof. Rudy Leibel

**Per Cent Body Fat Adjusted for Age**

- **+/+** (n = 56)
- **db/+** (n = 51)
- **db/ob** (n = 5)

**Leptin Threshold Effects**

Signal Threshold Impedance:
LEPR, CPE, POMC, AGRP, MC4R, etc.

**Bioenergetics of Reduced Body Weight**

Calories per Day Needed to Maintain Weight

- **Thin**
- **Average**
- **Heavy**
- **Obese**

The screen versions of these slides have full details of copyright and acknowledgements
Understanding Obesity Genes and Environment in the Determination of Body Weight
Prof. Rudy Leibel

CNTF Reduces Body Weights Long Term and Induces Cell Proliferation in the Hypothalamus

Investigators

Columbia University
Krista Vandenbome
Mike Rosenbaum
Dan Bloomfield
Rochelle Goldsmith
Sanobar Parkar
Wahida Karmally
Media Berghout
Dwight Matthews
Solveig Halldorsdottir

Rockefeller University
Jules Hirsch
Wendy Chung
Charles Mobbs

Mount Sinai Hospital
Yiying Zhang
Naoki Matsuoka
Loan Phan
Sharon Wardlaw
Judy Komer
Emerson Whittington

NYORC
Steve Heymsfield
Xavier Pi-Sunyer
Carol Bozzer
Harry Kislieff

Amgen Inc.

THANKS

Extreme and/or familial obesity
Obesity with short stature or developmental delay

RL232@columbia.edu